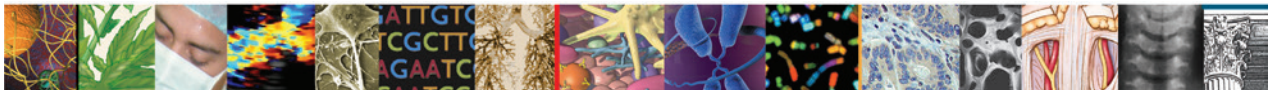

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Perspective

Collateral Benefits of Preventive Chemotherapy — Expanding the War on Neglected Tropical Diseases

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The collateral and extended effects of preventive chemotherapy, many of which were unanticipated, have reduced disease burdens and saved lives on a scale that appears to have exceeded the intended impact on seven neglected tropical diseases (NTDs) — the three major soil-transmitted helminth infections (ascariasis, trichuriasis, and hookworm infection), schistosomiasis, lymphatic filariasis, onchocerciasis, and trachoma.

The concept of integrated programs of mass drug administration (also referred to as preventive chemotherapy) was first proposed in the early 2000s, and such interventions now reach more than 1 billion people per year in low- and middle-income countries of Africa, Asia, and Latin America.[1] Implementation of the World Health Organization (WHO) preventive chemotherapy strategy has resulted in substantial reductions in the disease burden and disability-adjusted life years (DALYs, or lost years of healthy life) — as much as a 46% decrease in DALYs — attributable to the seven NTDs, allowing some countries to achieve their elimination targets for trachoma, lymphatic filariasis, and onchocerciasis. Moreover, it has led to cost savings for the world's poorest people, by reducing catastrophic health expenditures.[1]

Scientists and public health experts realized at the outset of this program that the primary drugs used for preventive chemotherapy, including albendazole or mebendazole, ivermectin, praziquantel, and azithromycin, might affect conditions beyond their originally intended targets. Now, nearly 15 years after mass drug administration for NTDs was first proposed, the existence of such collateral benefits can be verified (see table).

In an Australian aboriginal community, a single dose of ivermectin (200 μg per kilogram of body weight) delivered in two community mass drug administrations 12 months apart not only prevented ascariasis, trichuriasis, and hookworm infections, but also significantly reduced the prevalence of strongyloidiasis. A similar effect on strongyloidiasis was achieved in Cambodia with a single mass ivermectin administration. Ivermectin also reduces the prevalence of loiasis (human *Loa loa* infection) in places where both onchocerciasis and loiasis are endemic. A recently published clinical trial suggests that ivermectin could help reduce the prevalence of mansonelliasis in the Amazon, although it's less clear whether

Extended Targets of Medications Used for Preventive Chemotherapy against NTDs.

Drug	Original Targets	Extended Targets
Albendazole or mebendazole	Ascariasis Trichuriasis Hookworm infection	Oesophagostomiasis Strongyloidiasis
Ivermectin	Lymphatic filariasis Onchocerciasis	Scabies Strongyloidiasis Loiasis Mansonelliasis Malaria transmission
Praziquantel	Schistosomiasis	Foodborne trematodiases Taeniasis
Azithromycin	Trachoma	Yaws Child mortality

this effect could be replicated in Africa. In addition, mass administration of albendazole appears to have reduced the prevalence of oesophagostomiasis (*Oesophagostomum bifurcum* infection) in humans, even to the point of elimination in northern Ghana and Togo. Mass administration of single-dose praziquantel for schistosomiasis also appears to be effective for the treatment of opisthorchiasis (in Southeast Asia) and human tapeworm infections.

Furthermore, preventive chemotherapy is showing substantial collateral benefits for two neglected skin diseases — scabies and yaws.[2,3] Although the Global Burden of Disease Study does not provide estimates for yaws, it has revealed that scabies (and its associated secondary bacterial infections, especially impetigo) has one of the largest public health effects among the NTDs. Beginning in 2012, large-scale studies, including randomized clinical trials, conducted in the South Pacific and Africa showed the benefits of mass administration of ivermectin for scabies.[2] The International Alliance for the Control of Scabies has been leading global efforts to raise awareness about scabies and impetigo, promoting the addition of scabies to the WHO list of NTDs and highlighting mass drug administration as an appropriate intervention strategy.[2] Similarly, mass administration of azithromycin designed for trachoma elimination has shown enormous promise for the treatment and elimination of yaws.[3] A major study from Papua New Guinea in 2015 found that mass azithromycin administration substantially reduced the prevalence of yaws,[3] as did a single round of such treatment in Ghana.

More recent studies have shown that plasma containing ivermectin has the capacity to reduce transmission of *Plasmodium vivax* malaria, thanks to the drug's effects on the viability of both anopheles mosquito vectors and the malaria parasites themselves. In Kenya, among adults treated with both high-dose ivermectin and dihydroartemisinin–piperaquine, blood containing ivermectin was shown to reduce survival of *Anopheles gambiae* mosquitoes that fed on it, which suggests that this approach could also help in controlling *P. falciparum* malaria.[4] These results, though exciting, are still preliminary, and the question of whether mass administration of ivermectin in the appropriate doses for control of lymphatic filariasis and onchocerciasis might also reduce malaria transmission has yet to be investigated.

In 2009, in a trachoma-endemic area of Ethiopia, mass azithromycin administration was found to be associated with dramatic reductions in overall child mortality. The findings were considered astonishing, given that trachoma is not a fatal childhood infection, and it was hard to understand how a single dose of azithromycin would affect the outcome of serious bacterial coinfections such as pneumonia or diarrheal disease. But in a large, randomized follow-up study in Malawi, Niger, and Tanzania, the MORDOR (Macrolides Oraux pour Réduire les Décès avec un Oeil sur la Résistance) group confirmed that overall child mortality was lower among preschool children who received azithromycin.[5] The public health effect occurs primarily in the first 3 months after the distribution of the drug, which suggests that azithromycin could have substantial benefits if administered to populations more frequently than once, or even twice, per year. A follow-up MORDOR II study is planned for Burkina Faso to test these, and other, ideas.

Since the original drug packaging for the preventive chemotherapy strategy was proposed, some exciting possibilities have been identified for drug substitutions or additions. Among these possibilities are new anthelmintic agents, such as tribendimidine (for foodborne trematodiases and soil-transmitted helminth infections); the addition of either tribendimidine or oxantel pamoate to albendazole, to increase the efficacy of treatment for trichuriasis and hookworm; and moxidectin (re-

cently approved by the Food and Drug Administration) in place of ivermectin in some settings. A further proposed addition is nitazoxanide to target the intestinal protozoa giardia and cryptosporidium. Finally, recent studies have indicated that chemoprophylaxis with single-dose rifampin in household contacts of people with leprosy may reduce leprosy transmission and prevalence in some settings. These medications require additional clinical testing and regulatory approvals or operational research before they can be fully incorporated into the preventive chemotherapy package. New vaccines against NTDs are also under development.

One concern regarding mass drug administration, especially with azithromycin, is the potential emergence of drug resistance both to the intended target pathogens for trachoma, yaws, and leprosy and to colonizing respiratory and gastrointestinal pathogenic bacteria. So far, mass azithromycin administration has been shown not to elicit drug resistance in *Chlamydia trachomatis*, but it may elicit azithromycin-resistant yaws. Moving forward, it will be essential to monitor preventive chemotherapy programs for the possible emergence of drug-resistant respiratory and gastrointestinal bacterial pathogens, and anthelmintic drug resistance may also emerge. A further consideration is the integration of preventive chemotherapy for NTDs with approaches to preventing malaria and HIV/AIDS.[1] For example, the findings regarding ivermectin's effect on malaria may inspire greater interaction between NTD- and malaria-prevention programs, and there is also renewed interest in treating female genital schistosomiasis in adolescence as a strategy for preventing HIV/AIDS.

Expanding the public health impact of preventive chemotherapy would significantly increase years of healthy life for people in affected regions and would be highly cost-effective. The mass drug administration platform is a successful manifestation of universal health coverage, and the broader range of NTD-control strategies contributes to progress toward the United Nations' Sustainable Development Goals. Such assessments are key advocacy messages that encourage further investments in NTD programs, which deploy a proven strategy that reaches more than a billion of the world's most vulnerable people each year.

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